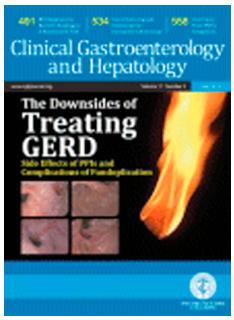
Accepted Manuscript



Development of Irritable Bowel Syndrome Features Over a 5-year Period

Egbert Clevers, Jan Tack, Hans Törnblom, Gisela Ringström, Koen Luyckx, Magnus Simrén, Lukas Van Oudenhove

PII: S1542-3565(18)30231-3
DOI: 10.1016/j.cgh.2018.02.043
Reference: YJCGH 55731

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 25 February 2018

Please cite this article as: Clevers E, Tack J, Törnblom H, Ringström G, Luyckx K, Simrén M, Van Oudenhove L, Development of Irritable Bowel Syndrome Features Over a 5-year Period, *Clinical Gastroenterology and Hepatology* (2018), doi: 10.1016/j.cgh.2018.02.043.

Development of Irritable Bowel Syndrome Features Over a 5-year Period

Egbert Clevers[1,2], Jan Tack[1], Hans Törnblom[2], Gisela Ringström[2], Koen Luyckx[3], Magnus Simrén[2,4], Lukas Van Oudenhove[1*]*

[1]Translational Research Center for Gastrointestinal Disorders (TARGID), University of Leuven, Belgium

[2]Dept of Internal Medicine & Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [3]Faculty of Psychology and Educational Sciences, School Psychology and Child and Adolescent Development, KU Leuven, [4]Center for Functional Gastrointestinal and Motility Disorders, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

* These authors contributed equally; shared senior authorship.

Grant support: This work is funded by the Swedish Medical Research Council (Grants 13409, 21691, and 21692), and by the Faculty of Medicine, University of Gothenburg.

Abbreviations: BIC (Bayesian Information Criterion), CBT (cognitive behaviour therapy), CRI (Coping Resources Inventory), FIML (full information maximum likelihood), GI (gastrointestinal), GSRS (Gastrointestinal Symptom Rating Scale), HADS (Hospital Anxiety and Depression scale), IBS (irritable bowel syndrome), OATT (oroanal transit time), PI-IBS (post-infectious irritable bowel syndrome), QOL (quality of life), VSI (visceral sensitivity index).

Correspondence: Egbert Clevers. KU Leuven, Targid - Herestraat 49, O&N1, Box 701 - 3000 Leuven, Belgium. E-mail egbert.clevers@kuleuven.be. Tel: +31 657353776.

Disclosures:

MS has received unrestricted research grants from Danone and Ferring Pharmaceuticals, and served as a Consultant/ Advisory Board member for AstraZeneca, Danone, Nestlé, Menarini, Almirall, Allergan, Albireo, Glycom and Shire, and as a speaker for Tillotts, Takeda, Menarini, Allergan, Shire and Almirall.

JT has given Scientific advice to Abide Therapeutics, AlfaWassermann, Allergan, Christian Hansen, Danone, Genfit, Ironwood, Janssen, Kiowa Kirin, Menarini, Mylan, Novartis, Nutricia, Ono Pharma, Rhythm, Shionogi, Shire, SK Life Sciences, Takeda, Theravance, Tsumura, Yuhan, Zealand and Zeria pharmacuticals, has received Research grant or support from Abide Therapeutics, Shire, Zeria and has served on the Speaker bureau for Abbott, Allergan, AstraZeneca, Janssen, Kiowa Kirin, Menarini, Mylan, Novartis, Shire, Takeda and Zeria.

LVO has received grant support from Nestlé and has given scientific advice to Grünenthal.

HT has served as Consultant/ Advisory Board member for Almirall and Allergan as a speaker for Tillotts, Takeda, Shire and Almirall.

GR, KL, and EC have no potential competing interests to disclose.

Author contributions: all authors were involved in planning/conducting the study, collecting/interpreting data, and drafting the manuscript. All authors have approved the final draft submitted.

Abstract

Background & Aims: There are few data from longitudinal studies of the gastrointestinal and psychologic features of irritable bowel syndrome (IBS). We studied within-person correlations among features of IBS, along with progression of gastrointestinal (GI) symptoms and quality of life, and factors associated with changes over time.

Methods: We performed a longitudinal study of 276 patients with IBS in Sweden (70% female; ages, 19–76 years) who completed questionnaires, each year for 5 years, about their GI symptom severity, quality of life, GI-specific anxiety, general anxiety, depression, and coping resources. We performed within-person correlation analyses, latent class growth analysis, and random-intercept cross-lagged panel analysis.

Results: Within-person correlations with GI symptom severity were strongest for quality of life (r=–0.56) and GI-specific anxiety (r=0.47). Progression of GI symptom severity was defined based on 3 classes; the class with the highest mean levels of GI, depression, and (GI-specific) anxiety symptoms at baseline did not improve over the 5-year period, contrary to the other classes. GI-specific anxiety was associated with an increase in GI symptom severity and decrease in quality of life 1 year later (P<.05) but other features of IBS were not.

Conclusions: In a 5-year study of patients with IBS in Sweden, we found 3 classes of GI symptom development. We found levels of GI-specific anxiety to associate with GI symptom severity and quality of life 1 year later. Clinicians should be aware of GI-specific anxiety in patients with IBS, to identify patients at risk for lack of long-term symptom improvement with standard medical treatment.

Keywords: functional gastrointestinal disorders; natural evolution; prediction; prognostic factor

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder (FGID) defined by chronic and/or recurrent abdominal pain associated with altered bowel habits.[1] However, IBS patients frequently suffer from psychological symptoms as well.[2] IBS prevalence is roughly 10%,[3] and, unfortunately, treatment and clinical management remains suboptimal.[4]

IBS symptoms are thought to wax and wane, without being progressive in the long term. Some studies have followed up IBS patients over several years, showing that the IBS diagnosis is often not continuously present over time,[5] and that symptom severity fluctuates substantially.[6, 7] Others found that improvements in symptom severity after three months predicted improvement after one year,[8] possibly indicating some consistency in symptom evolution. Improvement was also predicted by anxiety/depression at baseline. This seems counterintuitive, but may be an effect of regression-to-the-mean; patients with severe symptoms at baseline are more likely to improve on average whereas those with mild symptoms are more likely to worsen. Finally, one study reported that in individuals without IBS at baseline, anxiety levels predicted the onset of IBS at a follow-up of twelve years, while in individuals without anxiety at baseline, IBS predicted an increase in anxiety.[9] In summary, the evolution of IBS over time is complex and longitudinal studies are scarce and inconsistent, with a possible but uncertain role for psychological features, in line with the Rome IV conceptualization of FGIDs as disorders of gut-brain interactions.[10]

Further, most of the few published longitudinal IBS studies relied on two data points, whereas more data points are desirable to study symptom evolution. Besides, several psychological features have a cross-sectional association with IBS, such as GI-specific anxiety and coping resources,[11, 12] but their longitudinal relation with IBS symptom severity has not been investigated. Finally, IBS patients are heterogeneous, and results may render more meaningful on the within-person or subgroup level than on the between-person or total sample level. We therefore investigate: 1) longitudinal within-

person correlations of IBS features, and 2) evolution of GI symptoms and quality of life, subgroups thereof, and predictors of their changes over time.

Methods

IBS cohort

Patients

We used a Swedish longitudinal cohort of 276 adult IBS patients (≥ 18 years old), who were referred to our specialised unit for FGIDs from primary care or through self-referral. During an interview, the medical history was recorded and the diagnosis was made according to Rome II criteria, based on clinical presentation and additional investigations if considered necessary by the gastroenterologist (MS). However, the vast majority of patients who were referred from primary care had already undergone sufficient investigations to rule out other diagnoses with reasonable certainty. All patients were included in different studies assessing the pathophysiology of IBS,[13-17] although not in studies testing a standardised treatment. Exclusion criteria were abnormal results on standard screening laboratory tests, severe psychiatric, systemic, or other GI diseases, allergies, history of drug or alcohol abuse, and the inability to respond to questionnaires in Swedish. All patients gave written consent to participate after verbal and written information. The study protocol was approved by the Regional Ethical Review Board in Gothenburg prior to enrolment.

Questionnaires

Participants completed questionnaires once annually over five years, covering the following IBS features: GI symptom severity (Gastrointestinal Symptom Rating Scale, GSRS,[18] scale: 1 to 7), which queries the subdomains diarrhoea, constipation, abdominal pain, satiety, indigestion, and reflux; quality of life (IBS-QOL,[19] scale: 0 to 100), which specifically assesses the effect of IBS on quality of life; GI-specific anxiety (Visceral Sensitivity Index, VSI,[20] scale: 0 to 75), which queries fear and anxiety for GI symptoms as endogenous stressor; general anxiety and depression (Hospital Anxiety and Depression scale, HADS,[21] scale: 0 to 21); coping resources (Coping Resources Inventory, CRI,[22] scale: 60 to 240), which queries the way in which people handle stress in its broadest sense.

Other measures

At the start of the study, demographic information was collected, and all patients were subtyped based on the Rome II recommendation.[23] We also recorded if the onset of IBS occurred after a gastroenteritis, i.e. post-infectious IBS (PI-IBS). Participants underwent a barostat protocol, in which a balloon was distended in the rectum with 5 mmHg increments until the first report of pain (details elsewhere[24]). Finally, we quantified oroanal transit time (OATT) in a one-week protocol, where participants ingested ten radiopaque rings every morning, and on the seventh day the rings remaining in the bowel were counted (details elsewhere[16]). This number was divided by the number of rings per day to obtain OATT in days. A normal transit time was defined as 0.7–2.2 days for men and 0.9–4.2 days for women.[25]

Data analysis

Longitudinal within-person correlations of IBS features

We used R version 3.3.3[26] to compute within-person correlations between IBS features. Within-person correlations differ from regular Pearson correlations, which may miss processes relevant to the individual as exemplified in Supplementary Figure 1. Within-person correlations were computed by, for each participant, centering values on zero prior to computing regular Pearson correlations. Within-person correlations were visualised in a network using the R-package *qgraph*[27].

Symptom evolution and subgroups thereof

We used Mplus version 7.4[28] to perform two separate latent class growth analyses of GI symptom severity and quality of life. Simply put, this analysis searches for patient subgroups with common symptom evolution trajectories (i.e. "classes"). It does so based on overall severity level ("intercept"), linear development over time ("linear slope"), and u-shaped developments ("quadratic coefficients"). Technically, the number of latent trajectory classes was determined by the minimum Bayesian Information Criterion (BIC), given a statistically significant Lo-Mendell-Rubin adjusted test. Missing data was handled using the full information maximum likelihood (FIML) procedure.

We compared the classes by several baseline characteristics: age, sex, IBS subtype, PI-IBS status, rectal pain threshold, OATT, GI symptom severity, quality of life, GI-specific anxiety, general anxiety, depression, and coping resources. These comparisons were done using analysis of variance, Kruskal-Wallis, or chi-square tests as appropriate.

Prediction of rank order changes in GI symptom severity and quality of life

We used the R-package *lavaan*[29] to create so-called random-intercept cross-lagged panel models of psychological IBS features on the one hand (i.e. GI-specific anxiety, coping resources, general anxiety, and depression), and IBS outcomes on the other (i.e. GI symptom severity and quality of life). Simply put, these models analyse predictive relations between two variables. For example, it tests whether

anxiety at year 0 predicts GI symptom severity at year 1 while controlling for GI symptom severity at year 0. More formally, the technique is from structural equation modelling and investigates lagged associations while controlling for auto-regressive and within-time associations. The technique has been used particularly in social science to assess the directionality of effects (e.g. [30]). Here we selected a cross-lagged model that specifically accounts for heterogeneity.[31] Missing data was handled using the FIML procedure.

Results

IBS cohort

Of the 276 participants, 70% were female, and the age ranged from 19 to 76 years (median 39). All IBS features except coping resources had improving sample averages over the years, and all IBS features had some within-person variation (for example, the median within-person range of all IBS features was greater than one sample standard deviation). Descriptive statistics are in table 1. We compared participants who completed the study to those who dropped out (last available data point was used), and there were no statistically significant differences in any IBS feature (Supplementary Table 1).

Longitudinal within-person correlations of IBS features

GI symptom severity had strong within-person correlations with quality of life ($r=-0.56$, $p<0.001$) and GI-specific anxiety ($r=0.47$, $p<0.001$). By contrast, GI symptom severity had weaker within-person correlations with all other psychological variables: depression ($r=0.26$, $p<0.001$), general anxiety ($r=0.22$, $p<0.001$), and coping resources ($r=-0.15$, $p=0.02$). A network is shown in figure 1, with the full correlation matrix in table 2.

Symptom evolution and subgroups thereof

GI symptom severity evolved by three classes, representing 59, 119, and 36 IBS patients, respectively. The classes differed by overall baseline severity (i.e. intercept, p<0.001), and represent low, intermediate, or high GI symptom severity. To a lesser extent, there was also a difference in slope (p=0.002, i.e. the high GI symptom severity class did on average not improve, whereas the low and intermediate GI symptom severity classes did). The high GI symptom severity class was characterised by the youngest age (p=0.004), largest share of women (p=0.001), smallest share of PI-IBS (p=0.04), lowest rectal pain threshold at baseline (p=0.002), and the worst baseline score on all psychological IBS features except coping resources. Statistics are listed in table 3.

Quality of life evolved by four classes, representing 24, 43, 73, and 67 IBS patients, respectively. The classes differed by overall baseline level (i.e. intercept, p<0.001), and represent low, intermediate (2x), and high quality of life. The classes did not differ in evolution over time. The low quality of life class had the lowest rectal pain threshold at baseline (p=0.002) and the worst baseline scores on all psychological IBS features. Statistics are listed in table 3, and the trajectory classes are visualised in figure 2. The entropies of the two trajectory class solutions were 0.81 and 0.79, respectively.

Prediction of changes in GI symptom severity and quality of life

GI-specific anxiety predicted a change in both GI symptom severity (increase, p=0.031) and quality of life (decrease, p=0.050) one year later. Quality of life also predicted a change in GI-specific anxiety one year later (p=0.026). However, coping resources, general anxiety, and depression did not predict a change in either outcome. Random-intercept cross-lagged panel models are shown in figure 3, in which diagonal paths between variables are of particular interest, as they represent predictive

relations, whereas horizontal and vertical paths represent stability coefficients, within-time correlations, or correlated change.

Discussion

In this study, we show that GI symptom severity has strong within-person correlations with GI-specific anxiety and quality of life, but not with the other psychological IBS features. We further show that GI symptom severity is described by different trajectory classes. The class with the highest GI symptom severity on average did not improve over a five-year period. This class had, compared to the classes of low and intermediate GI symptom severity, the worst baseline scores on various psychological features and the lowest rectal pain threshold, and there was a high proportion of women but a low number of PI-IBS patients. Finally, we show that GI-specific anxiety can predict an increase in GI symptom severity, and decrease in quality of life one year later.

Longitudinal within-person correlations of IBS features

GI symptom severity had strong longitudinal within-person correlations with quality of life and GI-specific anxiety, but only weak correlations with the other psychological IBS features. The key message is thus twofold: first, GI-specific anxiety is positioned as a feature closely related to GI symptom severity. Second, general anxiety, depression, and coping resources are only weakly related to GI symptom severity on the within-person level, so that these psychological features and GI symptom severity are likely to stand in relative isolation. In one within-person analysis,[32] daily stress was not consistently associated with GI symptoms, which is in line with our conclusions. Labus *et al*,[33] although not using within-person correlations, showed that GI symptom severity was related more strongly to GI-specific anxiety than to other psychological IBS features. Wiklund *et al*[34] found GI

symptom severity to be more strongly correlated with quality of life than with general anxiety and depression. Lackner *et al*[11] presented similar results, albeit with different questionnaires. Wilpart *et al*[12] focused on coping resources, and found statistically significant associations between coping and all other tested IBS features. Finally, in the present study, quality of life was in the centre of the network, suggesting that quality of life in IBS is influenced by the totality of IBS features rather than GI symptom severity alone. It has been mentioned before that multiple independent predictors exist of reduced quality of life in IBS, i.e. both intestinal symptoms and psychological factors.[35]

Symptom evolution and subgroups thereof

Three classes of GI symptom severity evolution emerged, and four classes for quality of life. The classes differed chiefly by overall symptom severity ($p<0.001$), but, to a lesser extent, also by linear slope ($p=0.002$). The class of IBS patients with a high mean GI symptom severity had a high mean GI symptom severity in all follow-up years, and did on average not improve. That class was formed by relatively young women, having unselected rather than PI-IBS as well as high psychological symptom scores at baseline. It has been found previously that IBS is somewhat more prevalent with young age[36] and that PI-IBS patients have a slightly better long-term prognosis.[37] Moreover, it has been previously reported that a low rectal pain threshold is cross-sectionally associated with high GI symptom severity,[24] which is in agreement with our results. From our results one may theorise that the more symptomatic IBS patients are more refractory to treatment or sensitive to medication side-effects, and such patients require a specific management strategy. Few studies, however, have specifically portrayed the longitudinal development of IBS features, and those studies usually relied on two data points, so that development trajectories cannot be inferred.

Prediction of rank order changes in GI symptom severity and quality of life

GI-specific anxiety predicted an increase in GI symptom severity and a decrease in quality of life one year later. This brings forward GI-specific anxiety as factor of interest when assessing the severity of GI symptoms and predicting changes over time. No statistically significant predictive relations were found for the other psychological IBS features. Nevertheless, general anxiety and depression were from the HADS, which queries one's state over the past seven days, and as such may not reflect a general anxiety disorder or trait anxiety. It is still possible that trait anxiety can predict lack of improvement in GI-specific anxiety, GI symptom severity, and quality of life. Few studies investigated predictive relations between IBS features, although depression has been mentioned as negative predictor of treatment effect.[38] Labus *et al*[33] performed path analysis on IBS features, and found GI-specific anxiety to mediate the relation between psychological distress and GI symptom severity, although that analysis was cross-sectional and results are therefore difficult to compare with ours.

Since GI-specific anxiety predicted within-person changes in GI symptom severity and quality of life, it may be considered a key treatment target in IBS patients. Ljótsson *et al*[39] have recently shown in well-controlled clinical trials on internet-based cognitive behaviour therapy (CBT) that exposure and mindfulness components effectively reduce IBS symptoms and GI-specific anxiety, while improving quality of life. More specifically, they demonstrated that the effect on GI symptoms is mediated by a decrease in GI-specific anxiety,[40] supporting the present study in its notion that changes in GI-specific anxiety predict changes in IBS symptom severity. Further, they also confirm that GI-specific anxiety is treatable using CBT, which should therefore be considered a first-line treatment option in IBS patients with GI-specific anxiety. By contrast, IBS patients presenting with general anxiety or depression may require a different approach. More specifically, co-morbid anxiety and depressive disorders should obviously warrant referral to a mental health professional for psychopharmacological and/or or psychotherapeutic treatment, but based on our results, such treatment may have less impact on GI symptom severity or IBS-specific quality of life. The present study and its clinical implications thus highlight the heterogeneity amongst IBS patients and hence the potential need for individually tailored treatment.

One strength of the present study is that we use a longitudinal IBS cohort with six measurement points, allowing to monitor various IBS features over time. Furthermore, we reported within-person, rather than between-person correlations, giving a better understanding of the true relation between the IBS features. The study also has limitations. We had one data point per year, so that we could not quantify fluctuations within the year. Besides, latent class growth analyses are highly sensitive, introducing a risk for chance-based classifications.[41] It also cannot be stated that individual patients belong to a specific class, as class assignment is based on probability. To investigate symptom patterns of individual IBS patients and short-term fluctuations, different symptom monitoring approaches are needed, such as symptom diaries with a higher sampling frequency, although these will inherently be limited to shorter follow-up periods. Having information about treatment or medication side-effects would also have been desirable, in order to understand better why one class of patients does not improve over time. Furthermore, it is possible that patients are more likely to accept to be part of a study when they are in a symptomatic phase, thereby influencing the pattern of symptom evolution. Finally, the drop-out rate was rather high, although participants who completed or dropped out of the study did not differ on any baseline IBS feature.

In summary, we show that GI symptom severity can be described by different classes of evolution, and that these classes are associated with multiple baseline IBS-related features, such as psychological comorbidity, rectal sensitivity, post-infectious origin of IBS, age, and sex. GI symptom severity is strongly related to GI-specific anxiety, but not to general anxiety, depression, or coping resources, which are likely to stand in relative isolation from GI symptom severity. Finally, GI-specific anxiety can predict a change in GI symptom severity and quality of life one year later. Clinicians are recommended to be particularly attentive to GI-specific anxiety in IBS patients and refer patients for treatment targeting this key IBS feature, such as CBT.

Figure captions

Figure 1: Network of longitudinal, within-person correlations (r) between IBS features. Correlations of $|r|<0.3$ were made invisible for graphical purposes, but do influence the network. *: $p<0.005$.

Figure 2: Trajectory classes of GI symptom severity (left) and quality of life (right). Whiskers are minimum and maximum values. GI symptom severity: higher is worse; quality of life: higher is better.

Figure 3: Random-intercept cross-lagged panel models for GI symptom severity and quality of life. Diagonal paths between variables represent predictive relations. Non-statistically significant paths were made invisible for graphical purposes. Values are standardised coefficients.

References

1. Lacy BE, Mearin F, Chang L *et al*. Bowel Disorders. Gastroenterology. 2016 May;150(6):1393-407.e5.

2. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology. 2002 Apr;122(4):1140-56.

3. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012 Jul;10(7):712-721.e4. doi: 10.1016/j.cgh.2012.02.029.

4. Simrén M, Törnblom H, Palsson OS *et al*. Management of the multiple symptoms of irritable bowel syndrome. Lancet Gastroenterol Hepatol. 2017 Feb;2(2):112-122. doi: 10.1016/S2468-1253(16)30116-9.

5. Ford AC, Forman D, Bailey AG *et al*. Fluctuation of gastrointestinal symptoms in the community: a 10-year longitudinal follow-up study. Aliment Pharmacol Ther. 2008 Oct 15;28(8):1013-20.

6. Harvey RF, Mauad EC, Brown AM. Prognosis in the irritable bowel syndrome: a 5-year prospective study. Lancet. 1987 Apr 25;1(8539):963-5.

7. Waller SL, Misiewicz JJ. Prognosis in the irritable-bowel syndrome. A prospective study. Lancet. 1969 Oct 11;2(7624):754-6.

8. Mearin F, Badía X, Balboa A *et al*. Predictive factors of irritable bowel syndrome improvement: 1-year prospective evaluation in 400 patients. Aliment Pharmacol Ther. 2006 Mar 15;23(6):815-26.

9. Koloski NA, Jones M, Kalantar J *et al*. The brain--gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study. Gut. 2012 Sep;61(9):1284-90. doi: 10.1136/gutjnl-2011-300474.

10. Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. Gastroenterology. 2016 May;150(6):1262-79.e2.

11. Lackner JM, Ma CX, Keefer L *et al*. Type, rather than number, of mental and physical comorbidities increases the severity of symptoms in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol. 2013 Sep;11(9):1147-57. doi: 10.1016/j.cgh.2013.03.011.

12. Wilpart K, Törnblom H, Svedlund J *et al*. Coping Skills are Associated With Gastrointestinal Symptom Severity and Somatization in Patients With Irritable Bowel Syndrome. Clin Gastroenterol Hepatol. 2017 Mar 7.

13. Törnblom H, Van Oudenhove L, Tack J *et al*. Interaction between preprandial and postprandial rectal sensory and motor abnormalities in IBS. Gut. 2014 Sep;63(9):1441-9.

14. Jerndal P, Ringström G, Agerforz P *et al*. Gastrointestinal-specific anxiety: an important factor for severity of GI symptoms and quality of life in IBS. Neurogastroenterol Motil. 2010 Jun;22(6):646-e179.

15. Posserud I, Stotzer PO, Björnsson ES *et al*. Small intestinal bacterial overgrowth in patients with irritable bowel syndrome. Gut. 2007 Jun;56(6):802-8.

16. Törnblom H, Van Oudenhove L, Sadik R *et al*. Colonic transit time and IBS symptoms: what's the link? Am J Gastroenterol. 2012 May;107(5):754-60. doi: 10.1038/ajg.2012.5.

17. Posserud I, Syrous A, Lindström L, et al. Altered rectal perception in irritable bowel syndrome is associated with symptom severity. Gastroenterology. 2007 Oct;133(4):1113-23.

18. Svedlund J, Sjödin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988 Feb;33(2):129-34.

19. Hahn BA, Kirchdoerfer LJ, Fullerton S *et al*. Evaluation of a new quality of life questionnaire for patients with irritable bowel syndrome. Aliment Pharmacol Ther. 1997 Jun;11(3):547-52.

20. Labus JS, Bolus R, Chang L *et al*. The Visceral Sensitivity Index: development and validation of a gastrointestinal symptom-specific anxiety scale. Aliment Pharmacol Ther. 2004 Jul 1;20(1):89-97.

21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70.

22. Matheny KB, Curlette WL, Aycock DW *et al*. The Coping Resources Inventory for Stress. Atlanta, GA: Health Prisms; 1987.

23. Thompson WG, Longstreth GF, Drossman DA *et al*. Functional bowel disorders and functional abdominal pain. Gut. 1999 Sep;45 Suppl 2:II43-7.

24. Simrén M, Törnblom H, Palsson OS *et al*. Visceral hypersensitivity is associated with GI symptom severity in functional GI disorders: consistent findings from five different patient cohorts. Gut. 2017 Jan 19. pii: gutjnl-2016-312361. doi: 10.1136/gutjnl-2016-312361.

25. Sadik R, Abrahamsson H, Stotzer PO. Gender differences in gut transit shown with a newly developed radiological procedure. Scand J Gastroenterol. 2003 Jan;38(1):36-42.

26. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2017. URL https://www.R-project.org/.

27. Epskamp S, Cramer AO, Waldorp LJ *et al*. qgraph: Network Visualizations of Relationships in Psychometric Data. Journal of Statistical Software. 2012 48(4), 1-18. URL http://www.jstatsoft.org/v48/i04/.

28. Muthén LK, Muthén BO. Mplus User's Guide. Sixth Edition. 1998-2010. Los Angeles, CA: Muthén & Muthén.

29. Yves Rosseel. lavaan: An R Package for Structural Equation Modeling. Journal of Statistical Software. 2012;48(2):1-36. URL http://www.jstatsoft.org/v48/i02/.

30. Keijsers L, Loeber R, Branje S *et al*. Bidirectional links and concurrent development of parent-child relationships and boys' offending behavior. J Abnorm Psychol. 2011 Nov;120(4):878-89. doi: 10.1037/a0024588.

31. Hamaker EL, Kuiper RM, Grasman RP. A critique of the cross-lagged panel model. Psychol Methods. 2015 Mar;20(1):102-16. doi: 10.1037/a0038889.

32. Suls J, Wan CK, Blanchard EB. A multilevel data-analytic approach for evaluation of relationships between daily life stressors and symptomatology: patients with irritable bowel syndrome. Health Psychol. 1994 Mar;13(2):103-13.

33. Labus JS, Mayer EA, Chang L *et al*. The central role of gastrointestinal-specific anxiety in irritable bowel syndrome: further validation of the visceral sensitivity index. Psychosom Med. 2007 Jan;69(1):89-98.

34. Wiklund IK, Fullerton S, Hawkey CJ *et al*. An irritable bowel syndrome-specific symptom questionnaire: development and validation. Scand J Gastroenterol. 2003 Sep;38(9):947-54.

35. Zhu L, Huang D, Shi L *et al*. Intestinal symptoms and psychological factors jointly affect quality of life of patients with irritable bowel syndrome with diarrhea. Health Qual Life Outcomes. 2015 Apr 18;13:49. doi: 10.1186/s12955-015-0243-3.

36. Saito YA, Schoenfeld P, Locke GR 3rd. The epidemiology of irritable bowel syndrome in North America: a systematic review. Am J Gastroenterol. 2002 Aug;97(8):1910-5.

37. Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. Aliment Pharmacol Ther. 2007 Aug 15;26(4):535-44.

38. Rusu F, Dumitraşcu DL. Four years Follow-up of Patients with Irritable Bowel Syndrome. Rom J Intern Med. 2015 Jan-Mar;53(1):63-72.

39. Ljótsson B, Falk L, Vesterlund AW *et al*. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome--a randomized controlled trial. Behav Res Ther. 2010 Jun;48(6):531-9. doi: 10.1016/j.brat.2010.03.003.

40. Ljótsson B, Hesser H, Andersson E *et al*. Mechanisms of change in an exposure-based treatment for irritable bowel syndrome. J Consult Clin Psychol. 2013 Dec;81(6):1113-26. doi: 10.1037/a0033439.

41. Green MJ. Latent class analysis was accurate but sensitive in data simulations. J Clin Epidemiol. 2014 Oct;67(10):1157-62. doi: 10.1016/j.jclinepi.2014.05.005.

Tables

Table 1: Descriptive statistics of selected IBS features in the cohort. Values are means ± SD or counts.

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
$N_{NON\text{-}MISSING}$ (≈)	212	194	163	124	105	107

GI symptom severity	3.1 ± 0.8	2.9 ± 0.9	2.9 ± 1.0	2.8 ± 0.9	2.7 ± 0.9	2.7 ± 0.8
Quality of life	66 ± 17	73 ± 16	75 ± 17	77 ± 15	79 ± 15	78 ± 16
GI-specific anxiety	34 ± 17	29 ± 17	25 ± 16	24 ± 16	25 ± 16	25 ± 16
Coping resources	175 ± 22	169 ± 24	171 ± 24	171 ± 25	172 ± 25	172 ± 25
General anxiety	6.9 ± 4.3	6.1 ± 4.0	5.6 ± 4.0	5.5 ± 4.6	5.3 ± 4.0	5.6 ± 3.8
Depression	4.6 ± 3.6	4.1 ± 3.7	3.8 ± 3.6	3.9 ± 3.9	3.6 ± 3.6	3.9 ± 3.4

*Table 2: Correlation matrix of IBS features, with both within-person and between-person correlations. *: p<0.05, **: p<0.001.*

	GI symptom severity	Quality of life	GI-specific anxiety	General anxiety	Depression	Coping resources
GI symptom severity		-0.56**	0.47**	0.22**	0.26**	-0.15*
Quality of life	-0.66**		-0.64**	-0.30**	-0.39**	0.20*
GI-specific anxiety	0.56**	-0.72**		0.34**	0.34**	-0.14*
General anxiety	0.34**	-0.46**	0.43**		0.49**	-0.28**
Depression	0.29**	-0.50**	0.38**	0.64**		-0.40**
Coping resources	-0.18*	0.34**	-0.32**	-0.54**	-0.63**	

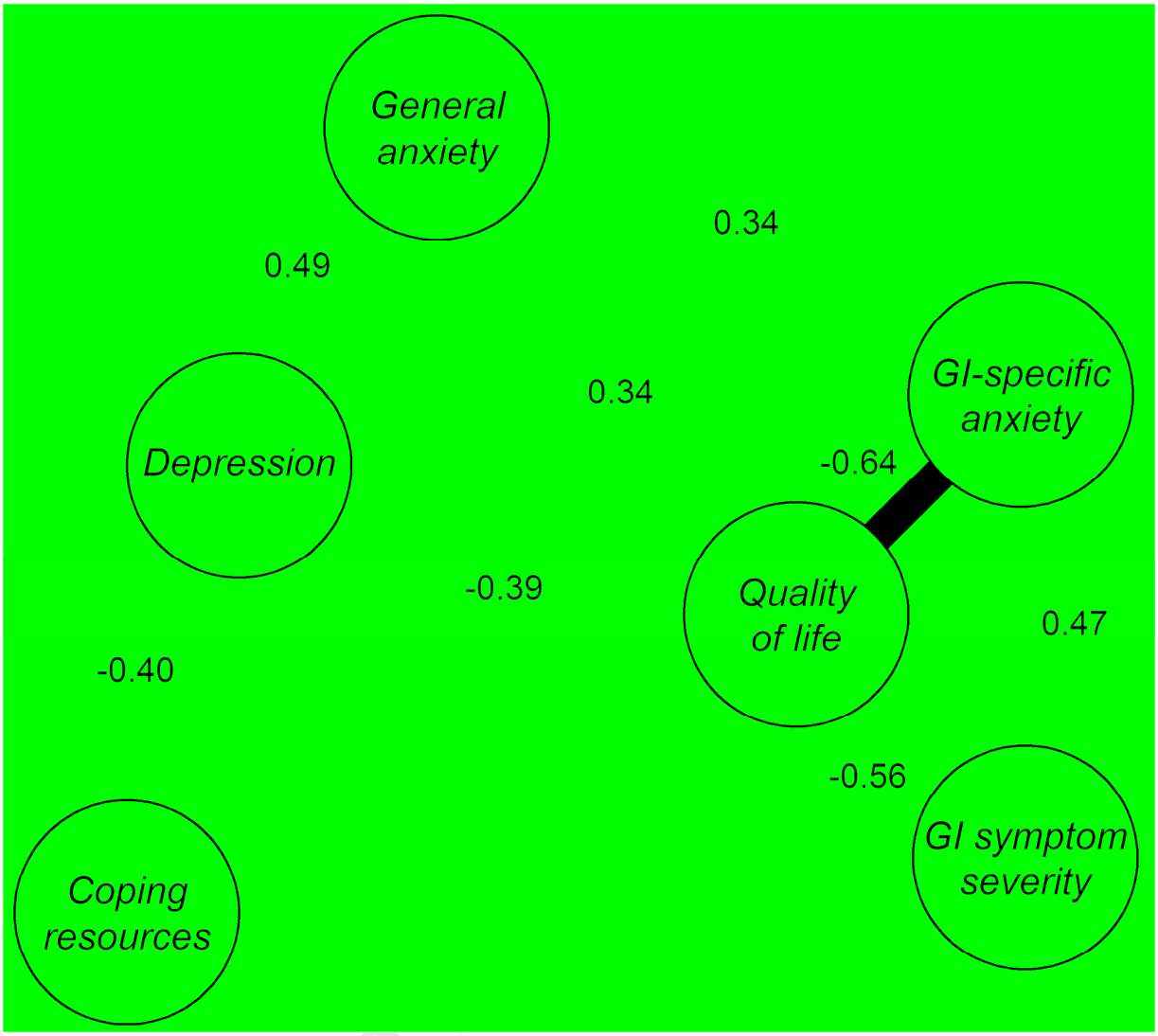
Between-person correlations

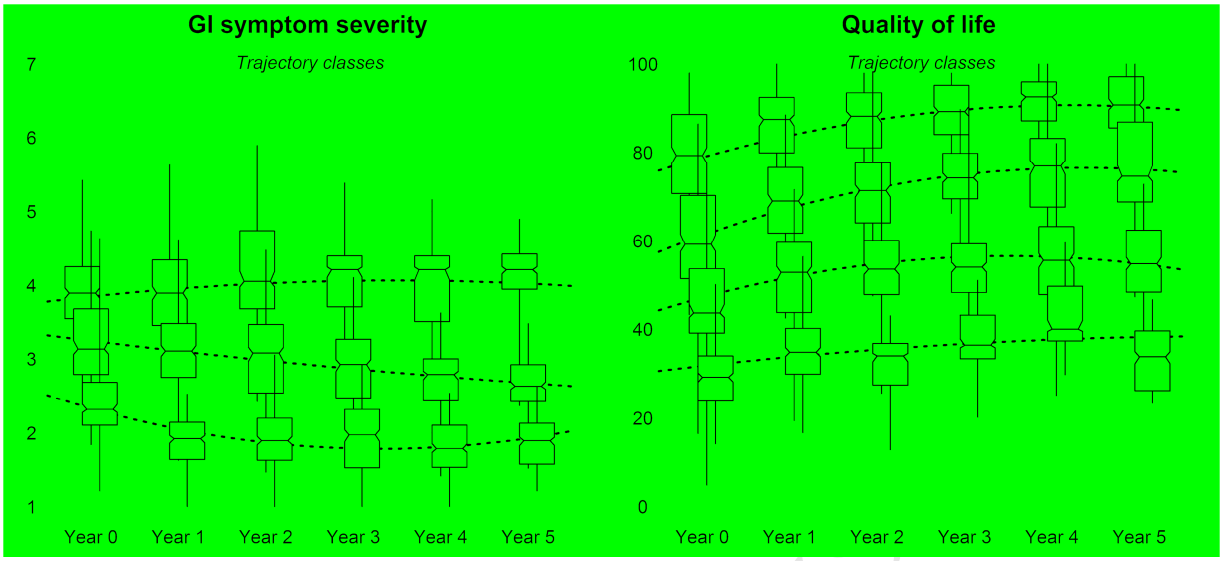
Within-person correlations

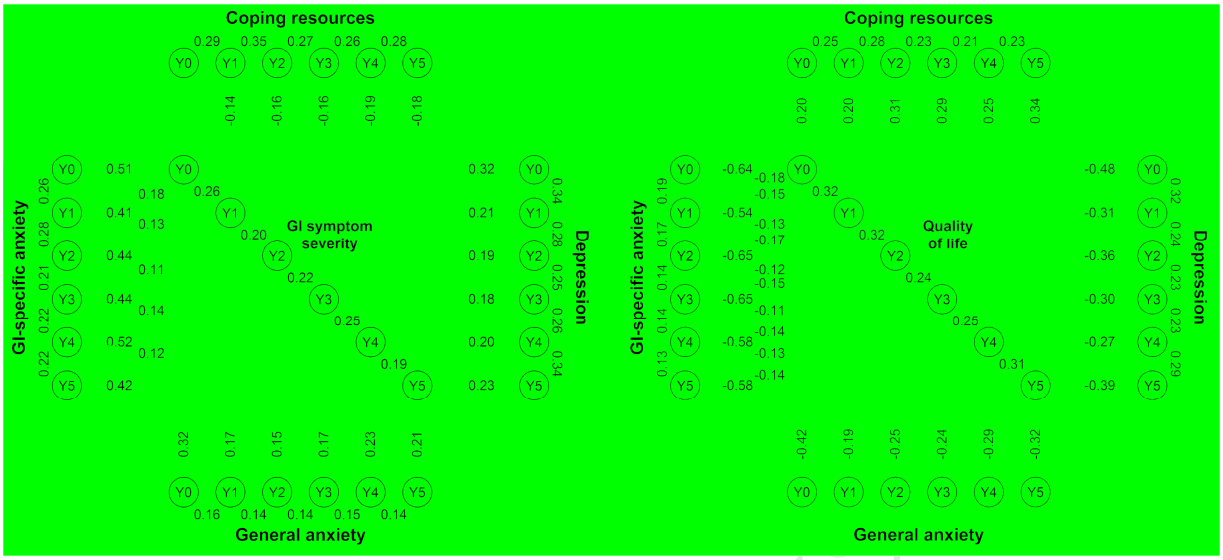
Table 3: Baseline descriptive statistics of the latent growth classes.

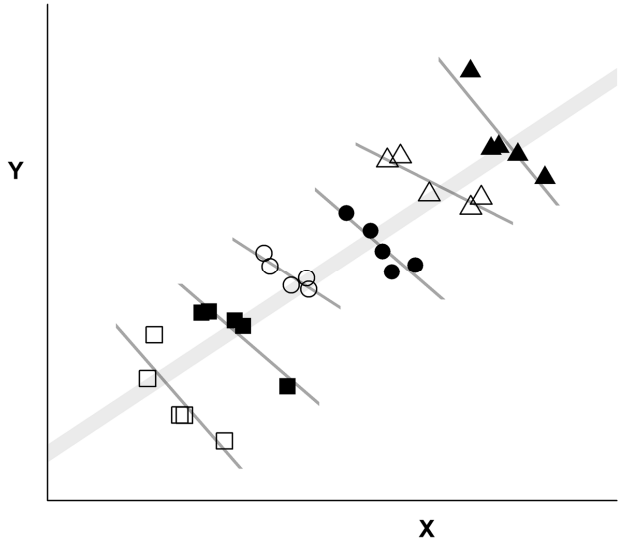
GI symptom severity	Quality of life

	Low	Mid	High	P	Low	Mid 1	Mid 2	High	P
N	59	119	36		24	43	73	67	
Intercept	2.3	3.4	3.8	<.001	32	47	61	78	<.001
Slope	-0.3	-0.1	0.1	.002	2	5	7	6	.24
Quadratic coefficient	0.05	0.01	-0.02	.03	-0.18	-0.76	-0.80	-0.66	.70
Age (years)	44 ±13	41 ±14	36 ±11	.004	38 ±12	40 ±15	42 ±15	41 ±12	.41
Female (%)	31 (53)	86 (72)	31 (86)	.001	18 (75)	31 (72)	54 (74)	43 (64)	.52
IBS-C (%)	11 (19)	23 (20)	7 (20)		4 (17)	8 (19)	12 (17)	15 (23)	
IBS-D (%)	29 (50)	47 (40)	9 (26)	.19	9 (39)	15 (36)	28 (39)	30 (45)	.78
IBS-A (%)	18 (31)	47 (40)	19 (54)		10 (43)	19 (45)	32 (44)	21 (32)	
PI-IBS (%)	7 (27)	6 (9)	1 (5)	.04	1 (7)	3 (16)	3 (7)	6 (21)	.28
IBS duration (years)	11 ±7	11 ±8	10 ±5	.78	10 ±5	10 ±5	10 ±7	11 ±7	.63
Rectal pain threshold (mmHg)	41 ±12	36 ±13	31 ±12	.002	30 ±10	32 ±13	36 ±12	40 ±15	.002
Accelerated transit (%)	6 (24)	6 (10)	7 (29)	.17	5 (26)	3 (12)	6 (15)	5 (20)	.56
Delayed transit (%)	3 (12)	14 (23)	5 (21)		6 (32)	4 (16)	8 (20)	4 (16)	
GI symptom severity	2.4 ±0.6	3.2 ±0.6	3.9 ±0.6	<.001	3.7 ±0.6	3.6 ±0.7	3.2 ±0.7	2.7 ±0.7	<.001
Quality of life	74 ±15	58 ±18	41 ±19	<.001	30 ±10	46 ±13	60 ±14	77 ±13	<.001
GI-specific anxiety	23 ±14	34 ±16	44 ±14	<.001	50 ±13	40 ±13	33 ±16	22 ±12	<.001
General anxiety	5 ±4	7 ±4	9 ±5	<.001	10 ±5	8 ±4	7 ±4	4 ±3	<.001
Depression	3 ±4	5 ±3	7 ±4	<.001	9 ±3	5 ±3	4 ±3	3 ±3	<.001
Coping resources	177 ±23	177 ±20	171 ±23	.29	167 ±20	174 ±23	175 ±22	181 ±19	.01


General anxiety
0.34
0.49
GI-specific anxiety
0.34
Depression
-0.64
Quality of life
-0.39
0.47
-0.40
-0.56
GI symptom severity
Coping resources







Supplementary Figure 1: Theoretical example of a relation between X and Y, with six participants and five data points per participant. Here, the regular Pearson correlation (thick line) is very different from the within-person correlation (thin lines). This discrepancy is an example of Simpson's paradox.

Supplementary Table 1: Comparison of drop-outs and non-drop-outs. For drop-outs, the last available value was used.

	Non-drop-out	Drop-out	P-value
GI symptom severity	2.9 ± 0.9	3.0 ± 1.0	0.69
Quality of life	69 ± 20	64 ± 23	0.33
GI-specific anxiety	28 ± 17	29 ± 19	0.70
Coping resources	169 ± 24	174 ± 24	0.32
General anxiety	5.7 ± 4.1	6.4 ± 4.6	0.46
Depression	4.1 ± 3.7	4.1 ± 3.8	0.98